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Review article

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Urinary tract infections: pathogenesis, host susceptibility and emerging therapeutics

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Abstract

Urinary tract infections (UTIs), which include any infection of the urethra, bladder or kidneys, account for an estimated 400 million infections and billions of dollars in health-care spending per year. The most common bacterium implicated in UTI is uropathogenic *Escherichia coli*, but diverse pathogens including *Klebsiella*, *Enterococcus*, *Pseudomonas*, *Staphylococcus* and even yeast such as *Candida* species can also cause UTIs. UTIs occur in both women and men and in both healthy and immunocompromised patients. However, certain patient factors predispose to disease: for example, female sex, history of prior UTI, or the presence of a urinary catheter or other urinary tract abnormality. The current clinical paradigm for the treatment of UTIs involves the use of antibiotics. Unfortunately, the efficacy of this approach is dwindling as the prevalence of antimicrobial resistance rises among UTI isolates, and the immense quantity of antibiotics prescribed annually for these infections contributes to the emergence of resistant pathogens. Therefore, there is an urgent need for new antibiotics and non-antibiotic treatment and prevention strategies. In this Review, we discuss how recent studies of bacterial pathogenesis, recurrence, persistence, host–pathogen interactions and host susceptibility factors have elucidated new and promising targets for the treatment and prevention of UTIs.

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Introduction

Urinary tract infections (UTIs) are a persistent and deadly global health problem and a considerable cause of health-care resource utilization. In 2019, an estimated 405 million infections and 267,000 deaths occurred globally owing to UTIs[1]. Incidence increases with age and shows a strong sex bias, with women having 3.6 times higher tendency to develop a UTI than age-matched men[1] and 50% of all women expected to develop at least one lifetime UTI[2,3], with symptoms including pain, urinary urgency and urinary frequency, all of which negatively affect the quality of life[4]. Although global analyses of health-care resource utilization owing to UTIs are scarce, the US Centers for Disease Control estimates that annually in the USA, there are 2.9 million emergency department visits and 3.5 million ambulatory visits for UTIs[5,6]. The costs of UTIs in the inpatient setting range from €5,700 per case in Europe[7] to US$13,000 per case in the USA[8], leading to an estimated annual expenditure of more than US$6 billion in the USA alone[8]. The available data almost certainly underestimate the true burden of UTIs; however, even with this caveat, the impact on individuals and society is clear.

The term urinary tract infection encompasses any infection of the urethra, bladder, prostate or kidneys. Bladder infection (cystitis) is the most prevalent. A majority of UTIs arise spontaneously in healthy patients and are considered uncomplicated UTIs. This is in contrast to a complicated UTI, which may refer to any number of patient-specific factors that increase the risk of adverse events, including the presence of a foreign body such as a urinary catheter or stent, anatomic urinary tract abnormality, pregnancy, diabetes, male sex or immunocompromised patient status[9]. The pathogenic mechanisms and treatment strategies differ between complicated and uncomplicated UTIs; here, we focus on uncomplicated UTI and catheter-associated UTI (CAUTI). In a subset of patients, most often women, an initial UTI will lead to a pattern of recurrent infections. Recurrent UTI (rUTI) is defined as having at least two UTIs within 6 months or at least three UTIs within 1 year (ref. 10).

Uropathogenic *Escherichia coli* (UPEC) bacteria are the most common pathogen responsible for approximately 75% of all uncomplicated UTIs and 65% of complicated UTIs. *Klebsiella pneumoniae, Staphylococcus* spp., *Enterococcus* spp., group B *Streptococcus, Proteus mirabilis, Pseudomonas aeruginosa* and *Candida* spp. can also cause UTIs (Fig. 1). Many of these species utilize common virulence mechanisms, such as adhesive pili, metal-ion acquisition systems and biofilm formation, to infect the bladder. Once an infection is established, a complex interplay between the pathogen, the host immune system, and other factors, including the vaginal and gut microbiota, determines the outcome of infection.

Antibiotics are the first-line treatment for UTIs of all types. However, rates of antimicrobial resistance (AMR) are rising, jeopardizing the efficacy of antibiotics. Fortunately, a wealth of new experimental therapies have been described in the past several years, including an antibiotic that recently completed phase III clinical trials and numerous promising vaccine candidates at various stages of clinical testing. Advances in basic UTI research continue to reveal promising therapeutic targets that will be tested in the years to come. This Review discusses the pathogenic cascades of the most common uropathogens and how this information is being used to design antibiotic-sparing drugs and vaccines. Specifically, this Review discusses UTI pathogenesis and bacterial persistence, the role of the immune system and other host susceptibility factors in modulating UTI outcome, and any advancements in developing new antibiotic-sparing drugs and vaccines based on host–pathogen interaction studies.

Bacterial pathogenesis

Much of what is known about the basic mechanisms of UTI pathogenesis comes from mouse models. A UTI begins with the introduction of a uropathogen, most commonly UPEC, into the urethra. UPEC bacteria establish a foothold in the bladder by binding to mannosylated terminal uroepithelial cells using type 1 pili. The bacteria then invade the cell and expand to form intracellular bacterial communities (IBCs) within the host cytosol. IBCs arise from the intracellular invasion of a single bacterium, which then undergoes clonal expansion[11] to resemble 'pods' of bacteria on electron microscopy, protruding into the bladder lumen. IBCs continue to express type 1 pili and produce a thick biofilm within their intracellular compartments[12] before exiting the IBC as long, filamentous rods that bridge to adjoining cells to restart a new IBC cycle[13] (Fig. 2). Although it is impossible to experimentally study the mechanisms of IBC formation in humans, human studies have identified exfoliated IBCs and filamentous bacteria in the urine of patients with UTI[14]. Additionally, IBCs have been directly visualized in bladder biopsy specimens[15], which supports the hypothesis that IBCs have a role in human infection. In response, the host activates an inflammatory response that leads to the shedding of infected epithelial cells, an upregulation of pro-inflammatory cytokines, and the recruitment of circulating immune cells such as neutrophils. In a subset of cases, bacterial infection can continue to ascend through the ureters to infect the kidneys (pyelonephritis), and from there, it can cause bacteraemia and sepsis (Fig. 2). At each step in this infection cascade, bacteria have evolved strategies to promote their own survival, and hosts have developed responses that attempt to neutralize bacterial virulence. The factors that uropathogens have evolved to colonize the urinary tract are diverse, both between and within taxa.

Efforts to define UPEC based on genomic signatures have not identified a common set of genes that plainly categorizes an *E. coli* strain as uropathogenic or non-uropathogenic. A study of 43 UPEC strains isolated from women with highly recurrent UTI has found that 60% to 75% of genes could be considered 'core' genes present in all analysed strains, whereas the remaining 25% to 40% of each genome was variable[16]. A recent study of 1,748 *P. mirabilis* strains, which included several hundred urinary tract isolates, has found an even greater level of diversity with core genes making up only 10% of the pangenome and UTI isolates spread evenly throughout the phylogenetic tree[17]. *Enterococcus faecalis* urinary isolates are also quite diverse[18]. Uropathogenicity defies easy genomic categorization because bacterial virulence factors and host susceptibility factors influence each other in complex ways[19]. For instance, the same UPEC strain may induce robust disease in one mouse genetic background while failing to colonize another[16]. Although no clear genetic pattern defines uropathogenicity, several trends in phylogeny, virulence and antimicrobial resistance have been observed. The vast majority of clinical UTI isolates have pathogenicity islands in their genomes that contain multiple virulence and/or antimicrobial resistance genes[20]. Within *E. coli*, putative urovirulence factors are substantially more prevalent in clade B2 compared to other *E. coli* clades. Clade B2 is responsible for most *E. coli* UTIs in the USA and Europe[16]. Three categories of genes frequently identified in pathogenicity islands and extensively studied in vitro and in mouse models include pilus systems, metal-scavenging proteins and biofilm formation.

Chaperone–usher pili

Pili are hair-like, proteinaceous extracellular fibres that extrude from bacterial membranes. Chaperone–usher (CUP) pili are molecular

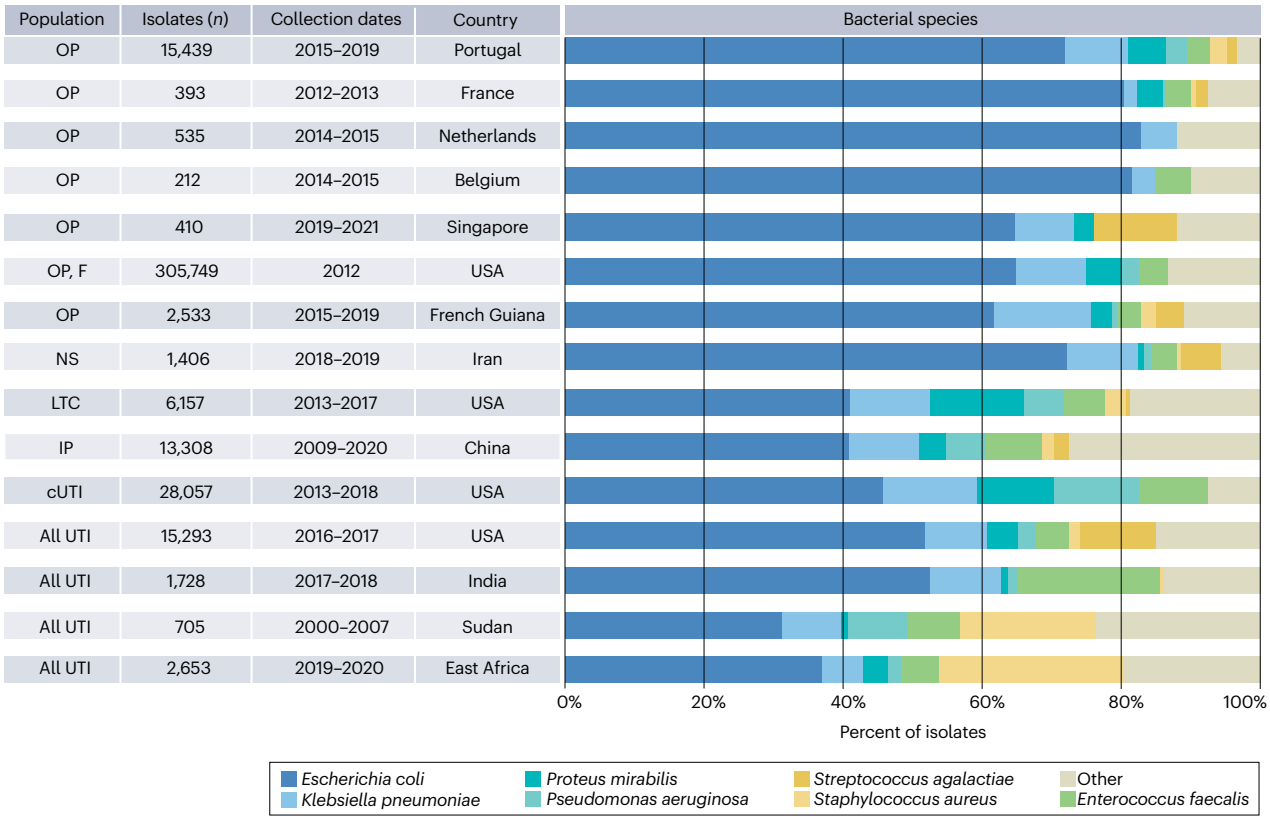

Fig. 1 | Epidemiology of UTIs. Uropathogenic *Escherichia coli* bacteria are the most common cause of urinary tract infections (UTIs) in most available data sets, although the proportion differs between geographic regions and patient populations. *E. coli* bacteria make up 75% to 80% of UTIs diagnosed in outpatient (OP) settings around the world. These UTIs tend to occur in females (F) and to be considered clinically uncomplicated. Other pathogens such as *Klebsiella pneumoniae*, *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Enterococcus faecalis* cause a larger proportion of complicated UTIs (cUTIs) and UTIs diagnosed in inpatient (IP) or long-term care (LTC) settings. The epidemiology of these pathogens reflects their pathogenic mechanisms: all four species are biofilm formers that opportunistically colonize urinary catheters used in high rates in cUTI and LTC patient populations. Notably, the proportion of UTIs caused by *E. coli* is lower and the proportion of UTIs caused by *Staphylococcus aureus* is much higher in sub-Saharan Africa than in other regions. Clinically important pathogens reported here in the 'other' category include *Staphylococcus saprophyticus*, *Acinetobacter baumannii* and *Candida albicans*[152–166]. NS, subtype of urinary tract infection not specified.

machines found in Gram-negative bacteria that catalyse pilus biogenesis. Each CUP gene cluster carries its own chaperone–usher machine that promotes the assembly of hundreds of highly related fibres. A single *E. coli* can encode up to 15 different types of CUP gene clusters. These consist of a major subunit that polymerizes to make up most of the length of the pilus and an adhesin subunit at the pilus tip, which mediates binding to different hosts, tissues and environmental habitats with stereochemical specificity. (For a detailed review of CUP pilus structure, see ref. 21.) A total of 38 unique CUP pili have been identified in the UPEC pangenome, with individual strains containing an average of 12 pilus operons[22]. *P. mirabilis* isolates encode an average of 14 CUP pili[23]. Of these, several have been found to have a role in UTI.

The most extensively characterized CUP pilus operon is *fim*, which encodes the type 1 pilus. The *fim* operon is present in most UPEC isolates and is also found in other UTI pathogens including species of *Klebsiella*[16,24]. The type 1 adhesin, FimH, facilitates bladder colonization by binding mannosylated glycoproteins that are abundant on the surface of bladder epithelial cells. Strains lacking FimH show attenuated virulence in mouse models of both UPEC and *K. pneumoniae* UTIs[25], suggesting that FimH is a promising target for antibiotic-sparing therapeutics. Other CUP pili facilitate binding to other tissues, including the kidney (P pili) and gastrointestinal tract (F17-like pili)[26,27]. The recently described Kpi pilus of *K. pneumoniae* promotes biofilm formation, tissue adherence and gut colonization[28].

Not all CUP pili have been linked to a known function. This is partly because it is challenging to discern the role of individual CUP pili owing to a high degree of redundance in some species. For example, in *P. mirabilis*, loss of a single pilus often has no deleterious effect on the ability of a bacterium to cause UTI in mouse models. It is only when the knockout strain is co-inoculated with a wild-type strain that a competitive defect becomes clear. The most extensively characterized CUP pilus in *P. mirabilis*, the mannose-resistant *Proteus* (MR/P) fimbriae, has a role similar to that of FimH and, like FimH, shows promise as a vaccine antigen[23].

Metal-ion acquisition systems

Bacteria compete for essential metal ions by expressing metallophores with very high affinities for their target metal[29]. Metallophores that

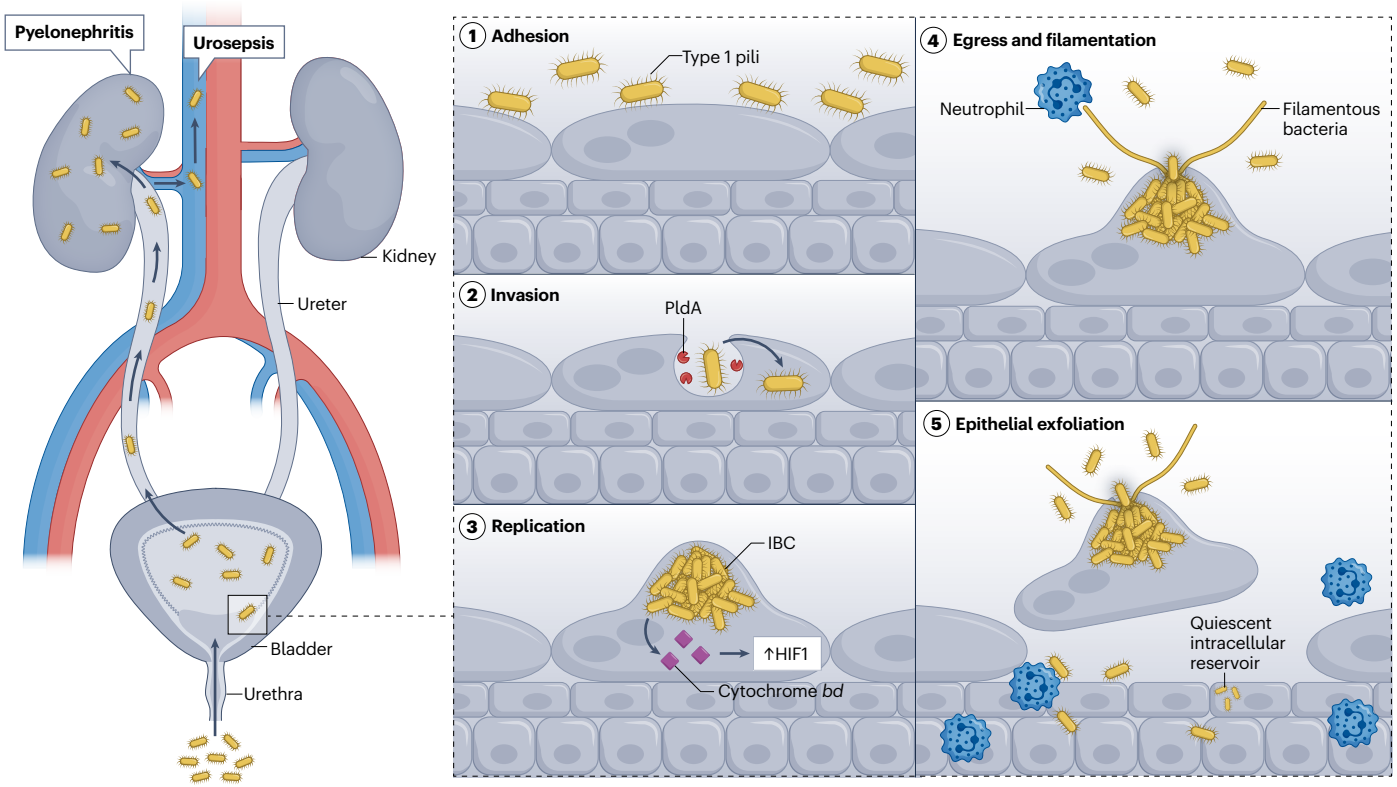

Fig. 2 | Pathogenesis of urinary tract infections. Bacteria ascend the urethra to reach the bladder. In a subset of cases, infection proceeds up the ureters to infect the kidneys (pyelonephritis) and may reach the bloodstream to cause bacteraemia and sepsis (urosepsis), which can be fatal. The inset on the right shows, from top to bottom, the progression of bladder infection through a cycle of bacterial adhesion, cellular invasion and egress. Uropathogenic *Escherichia coli* (UPEC) bacteria adhere to superficial facet cells using type 1 pili (stage 1). Once adhered, UPEC bacteria invade facet cells (stage 2). Initially contained within vesicles, UPEC bacteria upregulate the phospholipase PldA to overcome phosphorus starvation and escape into the cytosol[38], wherein they quickly form clonal intracellular bacterial communities (IBCs) (stage 3) that protrude into the bladder lumen[12]. *E. coli* express cytochrome *bd*, which binds cytosolic oxygen and induces host expression of hypoxia-inducible factor 1 (HIF1)[39]. This factor prevents apoptosis of the infected cell. The cycle repeats when facet cells burst and release filamentous cords of UPEC into the urine, which go on to infect nearby cells. Filamentous bacteria are resistant to phagocytosis and killing by recruited neutrophils[13] (stage 4). The host responds by rapidly exfoliating infected superficial cells; however, such a response exposes the underlying epithelial layers to bacteria, which can form quiescent intracellular reservoirs that later emerge as a resurgent infection[78] (stage 5).

are specific for iron are called siderophores. Uropathogens encode a number of siderophores and metallophores, including enterobactin, aerobactin and yersiniabactin, which have an important role in the iron-limited urinary environment[30]. A recent study has demonstrated that in vitro siderophore expression was the second most highly correlated phenotypic predictor of in vivo uropathogenicity[31]. UPEC have evolved mechanisms to facilitate iron acquisition even when siderophores are deactivated by host defences (for example, lipocalin-2, also called siderocalin, which binds and inactivates enterobactin). The ferric citrate transporter system, *fec*, is enriched in UPEC isolates compared to faecal strains and has been shown to be a UPEC virulence factor in vitro and in vivo[32]. Siderophore expression is also closely tied to pathogenicity in other bacteria, including *K. pneumoniae*, wherein salmochelin and aerobactin biosynthesis have been epidemiologically associated with virulence and mortality in humans[33].

Biofilm formation

The ability to form biofilms is strongly correlated with uropathogenicity across multiple clades. Biofilm formation in UPEC depends on both type 1 pili and the bacterial amyloid system, curli[34]. By contrast, *K. pneumoniae* biofilm formation depends on both type 1 and type 3 pili (encoded by the *Mrk* operon)[35]. Some uropathogens are known biofilm producers, but little is known about their biofilm formation mechanisms. *P. aeruginosa* virulence factors that have been hypothesized to have a role in biofilm formation include exopolysaccharides, amyloid-like fimbriae (Alf) and pyocyanin[36]. Exopolysaccharides, which have an important role in other niches, seem to be dispensable in the urinary tract. The secreted pigment pyocyanin, which gives *P. aeruginosa* its characteristic blue colour, is thought to contribute to biofilm formation in the bladder by cross-linking extracellular DNA[36]. *P. mirabilis* biofilms have a distinct structure characterized by the incorporation of mineral deposits. Urease expression by *P. mirabilis* increases the urine pH and precipitates struvite crystals, which become part of the biofilm matrix. This process requires both MR/P fimbriae and urease, and loss of either factor results in thinner and less robust biofilm formation. In addition to enhancing bacterial titres, these crystalline biofilms contribute to clinical disease because they are a nidus for urinary stone formation and can obstruct urinary catheters[23].

Other bacterial infection mechanisms

Studies interrogating the bacterial factors that have a role in persistence within the bladder cells have identified genes involved in the use of non-glucose carbon sources and iron scavenging[37]. Recent work in mouse models has connected *E. coli* expression patterns to their impact on host cells and has elucidated a mechanism through which intracellular *E. coli* prevents epithelial exfoliation[38,39]. When UPEC bacteria first invade a host cell, they are initially contained within a vesicle. The host responds by attempting to starve the intravesicular bacteria of phosphate, leading UPEC to express phospholipase PldA, which disrupts the vesicle membrane and facilitates escape into the host cytosol[38]. Once in the cytosol, UPEC within IBCs express the *E. coli* cytochrome bd, which depletes cytosolic oxygen. The decrease in available oxygen induces the expression of hypoxia-inducible factor 1 (HIF1), thereby suppressing apoptosis and reducing epithelial exfoliation[39]. These data explain why, in spite of the speed and magnitude of the immune response in early UTI, some infected cells resist exfoliation.

Dissecting the mechanisms of IBC formation has historically been challenging because of the severe bottleneck leading to IBC formation in mouse models; however, the recent development of a urine-tolerant, 3D in vitro human urothelial model capable of supporting IBCs opens new doors to investigating the intracellular processes at work[40,41].

Pathogenesis of catheter-associated UTIs

CAUTIs are a substantial problem among hospitalized patients and those living in long-term care facilities. UTIs make up 20%–50% of all health care-associated infections[42], and up to 97% of health care-associated UTIs occur in catheterized patients[43]. The prevalence of this disease reflects some of the unique pathogenic mechanisms used by CAUTI pathogens to colonize the surface of a urinary catheter. Catheters increase the likelihood that a uropathogen and/or opportunistic pathogen will be introduced into the bladder lumen, either during the catheter insertion process or by acting as a 'highway' for environmental, vaginal or faecal bacteria to migrate to the bladder. Most crucially for the pathogenesis of CAUTI, the catheter elicits a foreign body reaction in the bladder and urethra, causing inflammation and leakage of serum proteins into the bladder lumen. Fibrinogen, a serum clotting factor, and other host proteins bind the catheter surface[44]. Studies in both humans and mice have demonstrated that multiple CAUTI pathogens that would otherwise be unable to bind to the slick catheter surface can then take advantage of the adherent fibrinogen to colonize the catheter. Some pathogens express fibrinogen-binding pili, including *E. faecalis* (Ebp pilus), *Acinetobacter baumannii* (Abp1 and Abp2) and *Candida albicans* (Als1)[45–48]. *Staphyloccocus aureus* binds fibrinogen using the surface-expressed adhesins clumping factor A (ClfA) and B (ClfB)[49]. Other species, such as *P. aeruginosa* and *P. mirabilis*, also preferentially bind fibrinogen-coated regions of urinary catheters[44,50], although the mechanism of the interaction is less well described. Several of these pathogens, including *E. faecalis* and *A. baumannii* fail to establish infection in the non-catheterized murine bladder, highlighting the significance of the foreign body reaction to the course of disease[51,52].

Adding to the complexity, CAUTI is frequently polymicrobial. One study examining 19 long-term care residents over 7 months has found that 97% (226 out of 234) of urine collections grew more than one organism[53]. Another study that longitudinally sampled both urine and catheters from 55 patients has found that 80.1% (296 out of 366) of samples were polymicrobial[54]. The dynamics of species within and between samples reflect complicated positive and negative associations. For example, *Staphylococcus* species are negatively associated with both other Gram-positive and Gram-negative species and have higher tendency to be the lone catheter colonizer, whereas *Proteus* species have higher tendency to be found in the presence of *Morganella* or *Providencia* species[54]. To tease apart species–species interactions, groups of two to four species have been studied in vitro. For example, *E. faecalis* and *P. mirabilis* produce biofilms of greater biomass and mutually enhance antibiotic resistance when grown in co-culture in vitro[55]. Similarly, *E. coli* was found to enhance *E. faecalis* growth in nutrient-limited artificial urine medium[54]. These interactions appear to be context dependent and perhaps strain dependent. The relative benefit of co-culture in a four-species in vitro biofilm model depended on the degree of antibiotic exposure. Interactions that were initially negative in the absence of antibiotic (for example, between *P. mirabilis* and *E. coli*) actually enhanced resistance in the presence of ciprofloxacin[56]. These data highlight the importance of considering a multitude of physiologically relevant conditions when evaluating polymicrobial interactions in vitro. Additional investigation of the complex interactions between species will be required to identify new actionable therapeutic targets.

Host responses to acute UTIs

The bladder mucosal immune system has a pivotal role in defending against UPEC infections, integrating both innate and adaptive immunity. The innate immune system acts swiftly in response to microbial challenges compared to the adaptive immune system. When these innate defences are compromised or dysregulated, the susceptibility to pathogens increases.

The defences of the bladder against infection begin at the urothelial surface, wherein intracellular tight junctions and a dense coating of surface glycoproteins provide a physical barrier to infection. The kidney secretes high levels of the mannose-rich Tamm–Horsfall protein (also called uromodulin) into the urine, which acts as a physiologic mannose 'decoy' binding to type 1 pili and prevents binding to the epithelial surface[57]. Urothelial cells also constitutively secrete antimicrobial peptides such as cathelicidins[58], defensins[59,60] and secretory leukocyte protease inhibitor (SLPI) into the urine[61]. Urine secretory immunoglobulin A is less well investigated but may provide a degree of humoral immunity in the urinary tract[62]. Finally, bladder voiding has an important role in flushing bacteria out of the bladder.

If a uropathogen is able to overcome these intrinsic defences, the innate immune response rapidly recruits leukocytes to fight infection. The bladder senses the infection through pattern recognition receptors expressed by urothelial cells, including Toll-like receptor (TLR) 4 and 5, which sense bacterial lipopolysaccharide and flagellin, respectively[63,64]. When infection is detected, a robust pro-inflammatory programme is initiated, which triggers shedding of infected urothelial cells. Bladder-resident Ly6C$^-$ macrophages act as sentinels, secreting chemokines to recruit neutrophils, whereas recruited Ly6C$^+$ macrophages produce tumour necrosis factor (TNF), initiating a second wave of cytokines that trigger neutrophil transmigration to the urothelium[65]. This coordinated response between bladder-resident and recruited macrophages orchestrates an effective immune response against UTIs. Neutrophils have a critical role in the innate response through both phagocytosis of bacteria and expression of antimicrobial peptides such as α-defensins. However, prolonged and excessive neutrophilic activation can cause mucosal wounding that predisposes to UTI recurrence (Box 1). Other immune cells that exist in smaller quantities within the bladder, such as innate lymphoid cells, mast cells, eosinophils and mucosal-associated invariant T cells, are less well studied, but they may

Box 1 | COX2–TNF signalling and recurrence of UTIs

COX2 is an enzyme that converts arachidonic acid into prostaglandins, a family of key immune mediators. In the urinary tract, COX2 exerts many physiologic functions including promoting the expression of uromodulin and pre-pro-epidermal growth factor during kidney development[168] and expression of antimicrobial peptides psoriasin and β-defensin-2 in the setting of infection[169].

The upregulation of COX2 in response to infection has a key role in the innate immune response. COX2 is expressed by both urothelial cells and inflammatory cells and is inducible by TNF and the epidermal growth factor (EGF). In mice, transient TNF signalling during the early stages of UPEC infection supports bacterial clearance through rapid neutrophil recruitment and epithelial cell exfoliation, leading to effective resolution of infection[96]. However, uncontrolled and prolonged COX2–TNF expression during chronic infection induces mucosal wounding through excessive neutrophil infiltration. COX2 inhibition in C3H/HeN mice has been shown to reduce the intensity of both acute and recurrent urinary tract infections (UTIs) by lowering bacterial burdens and preventing severe neutrophilic inflammation[95,145]. Thus, COX2–TNF signalling represents a key part of the innate inflammatory cascade that must be carefully balanced to avoid counterproductive tissue damage.

A recent study has found that COX2 is also dramatically upregulated in the inflamed bladder regions of postmenopausal subjects with UTI. Prostaglandin E2, the product of COX2, was significantly elevated in the urine of women with recurrent UTI and predicted UTI recurrence more accurately than any other clinical variable either alone or in combination[170]. COX2 inhibition has not yet been attempted in humans; however, mechanistic studies in mice and evidence of human expression provide a strong rationale for future clinical investigations of COX2 inhibitors as a preventative agent for recurrent UTI.

have a role in the response to UTIs; these cell types have been recently reviewed elsewhere[66,67].

Although much ground has been gained in the area of innate immunity to UTIs, there is limited understanding of host and bacterial factors affecting a protective adaptive immune response. Patients with a history of UTI have serum antibodies specific to UTI antigens, such as iron receptor proteins, implying the existence of an adaptive immune response in these patients[68]. In addition, germinal centres are detectable in the bladder draining lymph nodes of mice with UTI[69]. However, the high recurrence of UTIs, even with the same bacterial strain, suggests that adaptive immunity fails to be protective in some individuals[70]. This effect probably depends to some extent on the specific strain of the infecting pathogen. C3H/HeN mice show susceptibility to same-strain recurrences caused by UPEC clinical cystitis isolate UTI89, but these are protected from same-strain recurrences caused by the clinical pyelonephritis and urosepsis isolate CFT073 (ref. 71). However, although a specific bacterial strain may be more or less adept at evading adaptive immune responses, there is a clear role for host differences as well. The relative contributions of different T cell subsets to UTI immunity have been investigated in two recent studies, which begin to explain why adaptive immunity often fails. In C57BL/6 mice, effector T cells become biased towards a T helper 2 (T_h2) (pro-epithelial repair) cell phenotype by day 3 post-infection, whereas levels of T_h1 (pro-bacterial clearance) cells remain flat, apparently in an effort to compensate for the massive epithelial exfoliation that occurs during the initial innate immune response[72]. This imbalance inhibits bacterial clearance during both initial and subsequent infections[72]. Intriguingly, it appears that only tissue-resident memory T (T_{RM}) cells are required for immune memory in response to a subsequent same-strain infection, whereas circulating memory T cells are dispensable[73]. Early antibiotic treatment interferes with the development of a robust T_{RM} cell response by reducing antigenic load[73]. These data highlight the delicate balancing act between the cell subsets mediating bacterial clearance, epithelial repair and immune memory formation. Too much or too little of any of these components dramatically alters the effectiveness of adaptive immunity. In addition, these studies have important implications for both potential immunomodulatory therapeutic strategies (for example, boosting T_h1 cell polarization) and clinical practice, wherein antibiotics are the mainstay of treatment but may impair immune memory formation. Additional studies are needed to integrate our understanding of the relative contributions of B and T cells and their subsets to the divergent UTI outcomes between bacterial strains and individual hosts.

Bacterial persistence and recurrence

In spite of the sophistication of the immune machinery of the bladder, UTI recurrence is a major problem that contributes to patient morbidity and the development of antibiotic resistance. Around 50% of women will have at least one lifetime UTI, 20% to 30% of these will go on to have a second UTI and 80% of these (2% to 3% of all women) will develop highly rUTI[2,74]. In a study performed in the UK, recurrences made up 50% of all diagnosed UTIs[75]. Recurrent UTI is a unique syndrome that is driven by a combination of bacterial and host factors. It is important to note that 50% of rUTIs are caused by the same strain that caused the initial UTI[76]. This suggests that the pathogen may have a reservoir within the host, possibly within the bladder itself, or within the vaginal or gut microbiota (Fig. 3).

Bacterial persistence within the bladder

The use of mouse models has allowed the elucidation of mechanistic details of UPEC cystitis. In addition to IBCs, which have a role during active UTI infection, studies have also demonstrated the existence of 'quiescent intracellular reservoirs'. These reservoirs are collections of vesicle-enclosed UPEC that remain inside superficial epithelial cells weeks after infection, when epithelial exfoliation and regeneration are complete. Quiescent intracellular reservoirs can seed a recurrent infection on subsequent epithelial insult[77,78]. Although initial studies have focused on UPEC, recent studies have demonstrated that multiple other uropathogens including *A. baumannii*[52] and *P. mirabilis*[41] can establish quiescent intracellular reservoir-like structures within murine bladder cells.

Role of the gut microbiome

It has long been recognized that UTI-causing strains are present in the gut of infected individuals[79], supporting the hypothesis that the gut acts as a reservoir. One study has found that a 1% relative abundance of *E. coli* or *Enterococcus* species in the gut increased the risk of *E. coli* or *Enterococcus* spp. bacteriuria by a hazard ratio of 2.8 compared to patients with lower relative abundances[80]. A 'bloom', defined as an increase in the relative abundance of UPEC within the gut of patients with UTI, may occur in the time period immediately preceding the onset of a UTI recurrence[81]. In this model, the gut microbiome contributes to

rUTI by permitting a higher dose of uropathogen to persist within the gut, thus, providing an increased opportunity for translocation from the gut to the urinary tract.

However, recent data suggest that this reservoir paradigm may be overly simplistic. Longitudinal sampling of the bladder and gut microbiota in women with and without a history of rUTI has revealed similar levels of *E. coli* carriage in both groups[82]. Rather than differing in the presence or phylogroup of the gut *E. coli*, the two cohorts were found to differ in the microbial richness and prevalence of butyrate producers in their gut microbiota, as well as in markers of systemic immunity[82]. This raises the hypothesis that the gain or loss of a microbiome member, and perhaps its metabolic products, could either create a more hospitable niche for uropathogenic *E. coli* compared to non-uropathogenic strains, or could directly alter *E. coli* gene expression to increase the likelihood of survival in the bladder. Importantly, antibiotic exposure in the rUTI group failed to deplete UPEC from the gut. These data suggest that patients with rUTI suffer not only from UPEC carriage but also from broader dysbiosis and immune dysregulation. Additional work is needed to fully understand the complex interactions of the gut–bladder axis[83].

Role of the vaginal microbiome

The vaginal microbiome also serves as a reservoir for uropathogens. Unlike the gut microbiome, wherein diversity is considered to correspond to gut health, the 'healthy' vaginal microbiome is dominated by a single *Lactobacillus* species. Vaginal dysbiosis is frequently characterized by an increase in both the diversity and the biomass of the vaginal microbiome, and these changes have been correlated with an increased risk of UTI[84]. Decades of clinical evidence reviewed elsewhere have demonstrated that vaginal colonization by UPEC, *Enterococcus* spp. and other uropathogenic bacteria occurs more often in women with rUTI than in healthy women[84]. Although the molecular mechanisms of this colonization are unclear, one study in mice has found that UPEC bacteria are capable of invading vaginal cells to form vaginal intraepithelial communities analogous to the bladder IBCs described in the section 'Bacterial pathogenesis'[85]. Although further investigations are warranted, existing data support the notion that the vagina and periurethral area may have a crucial role in facilitating the movement of pathogens towards the bladder.

However, just as the interplay of the gut–bladder axis is probably more complicated than previously appreciated, the role of the vaginal microbiome seems to be larger than simply serving as a reservoir. The emerging concept of 'covert pathogenesis', in which vaginal microorganisms modulate bladder infections by classical uropathogens such as *E. coli*, has been supported by several recent studies using mouse models. The common vaginal species group B *Streptococcus* and *Gardnerella vaginalis* both enhance UPEC UTI[86,87]. *G. vaginalis* alters urothelial cell transcriptional profiles, including the upregulation of pro-inflammatory pathways[88,89], which lead to increased urothelial exfoliation and an increased susceptibility to subsequent *E. coli* UTI[89]. Conversely, *Lactobacillus crispatus* may have a protective role in the bladder by enhancing type 1 interferon responses and promoting UPEC killing[90]. Because human studies routinely report the presence of both *Gardnerella* and *Lactobacillus* species in the urine of women with recurrent UTI (Box 2), these data provide important insights into the potential significance of vaginal species in the bladder.

Host susceptibility factors

There is significant heterogeneity in the outcome of UTIs, with some patients clearing the infection completely and others having multiple

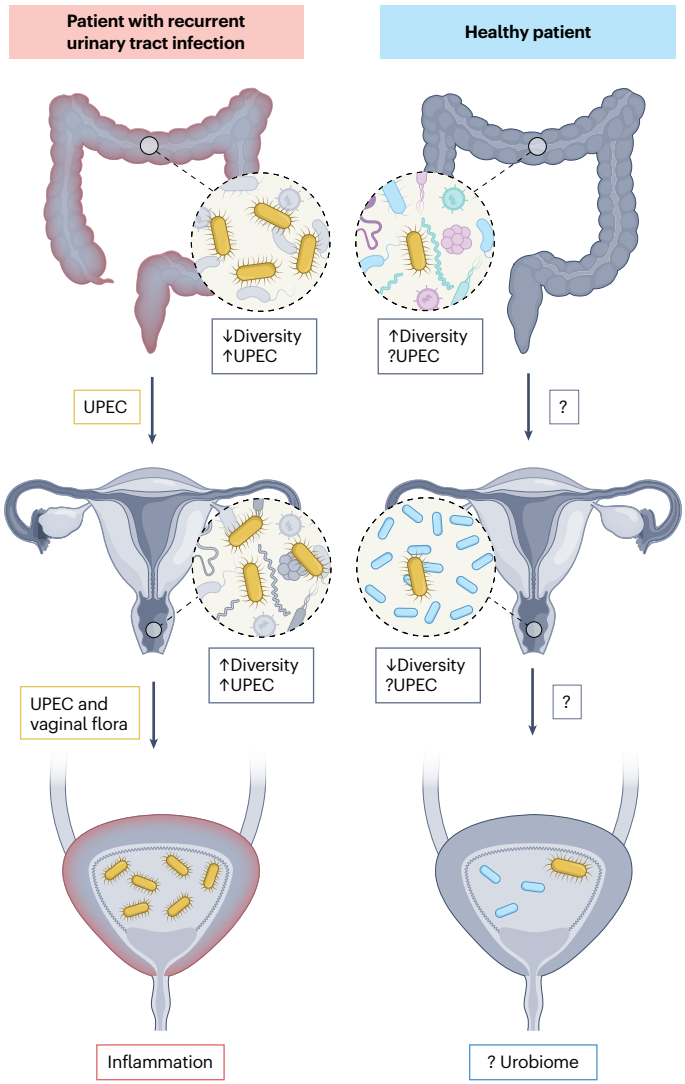

Fig. 3 | Model of the gut–vagina–bladder axis. Gut and vaginal dysbiosis may influence a urinary tract infection (UTI) through a variety of mechanisms. First, patients with recurrent UTIs are known to harbour reservoirs of uropathogenic *Escherichia coli* (UPEC) in their vaginas and gastrointestinal tracts[80,81,84]. A lack of colonization resistance caused by reduced community diversity may allow UPEC to bloom within the gut[81]. Conversely, in the vagina, a 'healthy' microbiome is typically dominated by a single *Lactobacillus* species that prevents or minimizes colonization by uropathogens (right panel); an increase in the diversity of the vaginal microbiome is associated with a higher risk of UTI (left panel). A higher dose of UPEC in the gut and the vagina increase the likelihood of transmission to the bladder, potentially leading to increased inflammation and development of UTI. Changes to microbiota structure in the gut (for example, a reduction in butyrate-producing bacteria[82]) could induce changes in UPEC gene expression, perhaps enhancing UPEC fitness in the bladder. Inoculation of other microbiota members may have a role in 'covert pathogenesis' of UTI by modulating the host response to UPEC in the bladder[84]. Pre-existing bladder colonization by the 'urobiome' may also have a role in the development of UTI[167]. Finally, the immune responses in the gut, vagina and bladder may influence each other at a systemic level. Arrows pointing up or down in front of a word indicate the direction of an event (increase or decrease). Question marks indicate where the direction and/or degree of an association is uncertain.

Box 2 | The urinary microbiome

For most of the last century, urine has been regarded as sterile, and the detection of common vaginal, gut or skin flora in urine cultures has been dismissed as contamination. However, within the last 15 years, an emerging body of literature has described the presence of a urinary microbiome or 'urobiome'. Early investigations of the urobiome used mid-stream urine samples[171,172], but the field quickly moved to establish transurethral catheterization as the preferred method for urobiome sampling to minimize the potential for contamination by vaginal or skin flora[173]. This decision is supported by studies comparing first-catch, mid-stream and catheterized urine samples from the same patient. These studies have demonstrated that catheterized samples have reduced alpha-diversity compared to spontaneously voided samples, with a smaller number of genera detected and differences in relative abundance[174].

Several 'urotypes' have been described in studies analysing catheterized urines. *Lactobacillus*-dominated urotypes are the most commonly reported within and between studies[167]. Other reported urotypes include *Gardnerella*, *Streptococcus*, *Escherichia* species and a mixed urotype characterized by multiple genera[175]. The clinical significance of these different urotypes is unclear. However, a loss of *Lactobacillus* spp. in the bladder has been associated with an increased risk of urinary track infection (UTI) following urogynaecologic surgery[176]. Notably, the urinary microbiome of premenopausal and postmenopausal women differ, with postmenopausal women having less tendency to be *Lactobacillus* dominated; this may have a role in the rise of UTI with age[177].

Additional studies are needed to better understand which species are present in the urobiome of different patient groups (for example, men, children, women with recurrent UTI and patients with urologic abnormalities), the significance of these taxa, and the mechanisms through which they may protect against or predispose to urinary conditions such as UTI.

recurrences. This observation has prompted researchers to search for specific host factors that may modulate susceptibility, revealing evidence for the roles of host genetics[91], biological sex[92] and age[93]. However, until recently, biological explanations for the most significant UTI risk factor, a history of prior UTI, were limited. Recent insights from a mouse model of recurrent cystitis and from an in vitro model of urothelial stem cells have begun to shed light on the mechanism of this association.

In C3H/HeN mice, the outcome of an initial UTI strongly correlates with the response to subsequent challenges[94,95]. Mice that spontaneously resolve the first infection (resolved mice) become resistant to rUTIs, whereas those progressing to chronic cystitis (sensitized mice) are more susceptible to rUTI upon challenge. Examination of the mouse bladder epithelium has revealed that the bladder epithelium undergoes differential inflammation-induced remodelling depending on disease history, either increasing or decreasing susceptibility to rUTIs. Resolved and sensitized mice had distinct morphological, proteomic and transcriptomic changes within their epithelium after initial infection and recovery. Notably, susceptibility to rUTI was strongly implicated in different dynamics of TNF and cyclooxygenase 2 (COX2) response in the bladder[96]. Resolved mice exhibited resistance to rUTIs owing to an accelerated and transient TNF–COX2 response, which facilitates rapid infection elimination and mucosal healing. By contrast, sensitized mice are highly susceptible to rUTIs, characterized by sustained TNF–COX2 expression, leading to excessive neutrophil transmigration and mucosal wounding. Selective COX2 inhibition was shown to protect sensitized mice against severe recurrent cystitis[95].

Recently, epigenetic changes in the bladder epithelial stem cells were discovered to dictate these differential bladder remodelling phenotypes during spontaneous resolution of infection and chronic cystitis[97]. Epigenetic analyses of urothelial stem cell lines from mice with different histories of UPEC infection have revealed that differences in infection history led to distinct chromatin accessibility, closely linked with variations in DNA methylation and histone modifications. Significant epigenetic changes in inflammatory sensor genes such as *Casp1* and *Ptgs2os2* suggest a potential mechanism by which these sensor genes are primed on initial chronic infection and may allow faster response to subsequent infection. Although increased expression of *Casp1* has a protective role during recurrent infection, it is often overcome by COX2-mediated inflammation, leading to the development of rUTIs. Notably, increased expression of the *Ptgs2os2* gene, which encodes LincRNA-COX2, a positive regulator of Ptgs2 expression and general inflammation[98], potentially contributes to sustained COX2-mediated inflammation and mucosal wounding during chronic cystitis. Overall, a history of chronic infection can reprogramme the urothelial epigenome, leading to urothelial remodelling and increased host susceptibility to future UPEC infection (Fig. 4).

Treatment and prevention of UTIs

Currently, antibiotics are the clinical standard-of-care for UTIs in the USA. The Infectious Disease Society of America and European Society of Microbiology and Infectious Diseases, which develop and publish joint treatment guidelines, recommend empiric treatment with nitrofurantoin, fosfomycin or trimethoprim–sulfamethoxazole for uncomplicated cystitis in patients at low risk of antibiotic resistance[99]. These guidelines are undergoing review and revision with an anticipated release date of fall or winter 2024 (ref. 100).

However, the current status of antibiotics as the front-line treatment for UTIs depends on a reasonable expectation of efficacy, which is being eroded as the prevalence of AMR rises. UTIs account for approximately 15% of all antibiotic prescriptions in the USA, with an estimated 3.7 million being inappropriate and not in line with clinical best practice guidelines[101]. In addition to increasing antibiotic use in general, there is also a growing tendency for UTIs to carry antimicrobial resistance genes. UTIs are now the fourth most common cause of deaths associated with antimicrobial resistance, and five out of the six top pathogens implicated in AMR-associated deaths are common UTI pathogens[102]. Thus, there is an urgent need to prevent UTIs and develop new treatments that minimize the use of antibiotics. As follows, we discuss emerging therapies that build on new knowledge of bacterial and host targets to prevent or treat UTIs. These therapies are summarized in Table 1.

Pathogen-targeted therapeutics

Antibiotics. Two new antibiotics have recently been evaluated for the treatment of UTIs. Gepotidacin is a first-in-class DNA gyrase inhibitor[103,104] that completed phase III clinical trials for the treatment of uncomplicated UTI in 2022. The group treated with gepotidacin produced microbiological and clinical responses at similar rates to the control group treated with nitrofurantoin with no reported safety events.

In one of the two phase III studies, gepotidacin even demonstrated superior therapeutic response (a combined measure of microbiological and clinical outcomes) over nitrofurantoin[105]. Another antibiotic, the oral carbapemen tebipenem pivoxil hydrobromide, recently exhibited clinical non-inferiority compared to intravenous ertapenem in a phase III clinical trial for the treatment of complicated UTI and pyelonephritis[106]. If approved by the Food and Drug Administration, these antibiotics will be important tools in the clinical arsenal. However, resistance against both gepotidacin[107] and tebipenem[108] has already been described, underlining the ongoing need for non-antibiotic options with lower resistance potential. Bacteriophage therapy and the urinary antiseptic methenamine hippurate have also recently been evaluated for UTI and have shown clinical efficacy against antibiotic-resistant infections, although additional study is needed (Table 1).

Anti-adhesives. The adhesive pili expressed by UPEC and other uropathogens are an attractive target for antibiotic-sparing UTI therapeutics because such molecules will not lead to cell death and, therefore, may evade typical selective pressure towards resistance. Theoretically, treatment with a compound capable of blocking the interaction between the pilus and its ligand should prevent bacterial adhesion to urothelial cells and facilitate expulsion in the urine. D-Mannose and cranberry products are two natural products with in vitro FimH-blocking properties that have recently been assessed for clinical efficacy. Cranberry products also contain proanthocyanins that block P pili[109]. Although a systematic review and a recent large randomized controlled trial have found no evidence to either support or refute the efficacy of D-mannose[110,111], a meta-analysis of 26 randomized controlled trials and a combined 6,211 participants has concluded that there is moderate-certainty evidence that cranberry products reduce the risk of symptomatic UTI[109].

A limitation of D-mannose as a treatment strategy is its relatively low affinity for the UPEC type 1 pilus adhesin, FimH. Advances in structure-based design have facilitated the development of glycomimetic compounds termed 'mannosides', which bind to FimH with 10^6-fold greater potency than D-mannose. Mannosides have shown promise in vitro and in animal models, wherein they reduce bladder bacterial burden by up to 4 logs within 6 h of oral administration[112]. The mannoside compound GSK3882347 has been selected for clinical development and is currently in phase I clinical trials to assess its safety and tolerability[113]. Although human efficacy data will not be available for some time, mannosides represent a promising strategy for UTI treatment.

Blocking iron scavenging. Several proteins involved in bacterial iron scavenging have been tested as vaccine targets for UTI (Table 1); however, a consistent challenge has been a lack of immunogenicity.

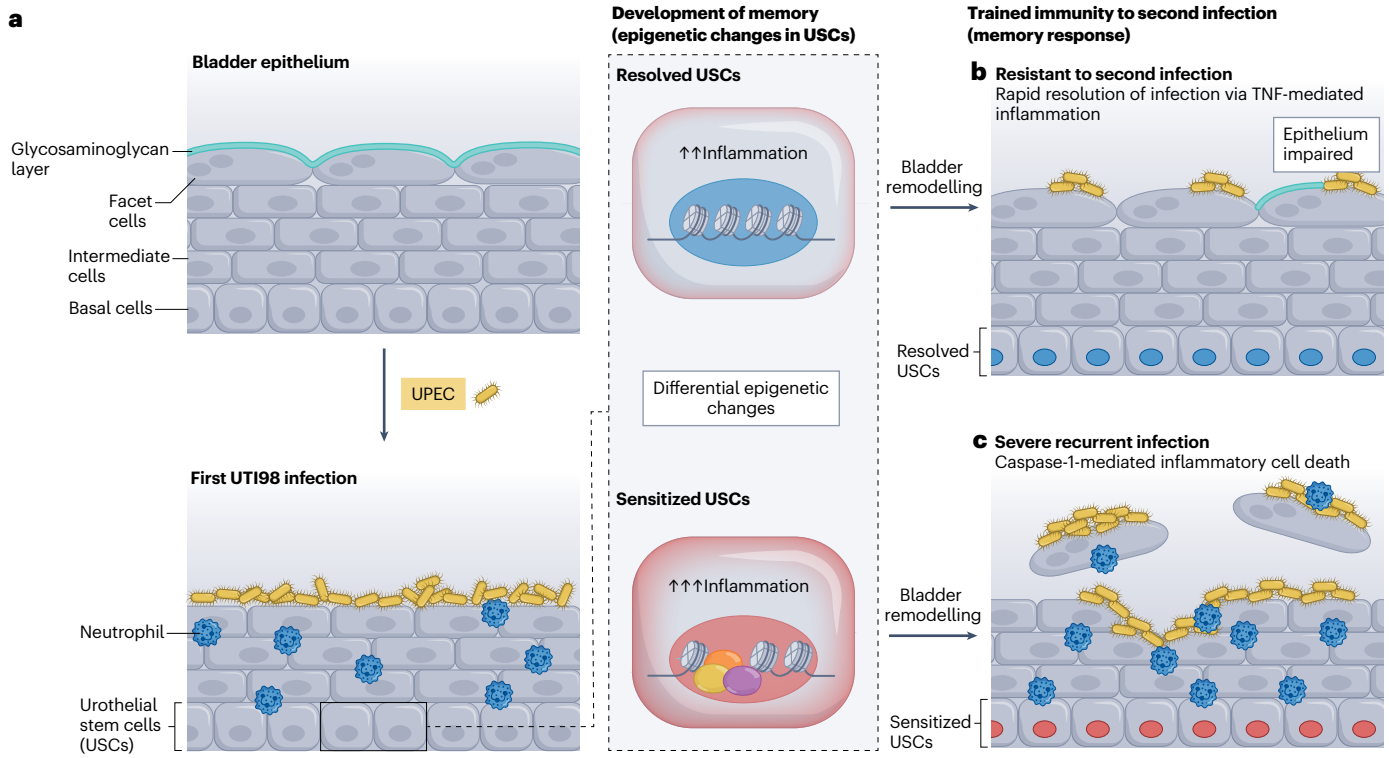

Fig. 4 | Model for bladder epithelial stem cell remodelling and trained immunity. a, On initial infection by uropathogenic *Escherichia coli* (UPEC), the urothelium of a C3H/HeN mouse either resolves infection spontaneously (resolved) or develops chronic cystitis (sensitized). While both resolved and sensitized epithelia undergo inflammation, sensitized experiences more severe inflammation, indicated by a greater number of arrows. Elevated neutrophil infiltration from mucosal tissue during initial infection predicts the development of chronic cystitis[94]. Resolved and sensitized urothelial stem cells (USCs) develop unique infection memories through differential epigenetic changes in their chromosomes. During recovery periods after antibiotic treatment, resolved and sensitized USCs dictate differential bladder remodelling while regenerating the urothelium, depending on disease history, which leads to different trained immunity to secondary UPEC infection. **b**, The resolved urothelium is resistant to secondary UPEC infection owing to an accelerated and transient tumour necrosis factor (TNF)-mediated inflammatory response facilitating clearance of infection and mucosal healing. **c**, The sensitized urothelium is highly susceptible to developing severe recurrent infection owing to sustained TNF–COX2 expression and caspase-1-mediated inflammatory cell death[97].

Table 1 | Emerging therapeutics for UTIs

Intervention	Disease target	Status	Evidence	Refs.
Antibiotics				
Gepotidacin	uUTI, rUTI	Phase III complete	Clinical non-inferiority compared with nitrofurantoin in two of two trials; superior therapeutic response in one of two trials	105,107
Tebipenem pivoxil hydrobromide	cUTI, pyelonephritis	Phase III complete	Clinical non-inferiority compared to intravenous ertapenem	106,108
Anti-adhesives				
D-Mannose	uUTI, rUTI	Multiple RCTs available	No benefit of D-mannose for the prevention of rUTI	110,111
Cranberry	rUTI	Multiple RCTs available	Cranberry consumption reduces the risk of UTI (RR 0.70, 95% CI 0.58 to 0.84), no effect on gut microbiome	109
Mannoside	uUTI, rUTI, CAUTI	Phase I trials ongoing	Reduction in bladder bacterial titres in mice; depletion of UPEC from the murine gut	27,112,113,137
Galactoside	uUTI, rUTI	Preclinical	Reduction in bladder bacterial titres in mice	138
Vaccines				
ExPEC9V	uUTI, cUTI, rUTI, urosepsis	Phase III trial enrolling	Results from a phase Ib study showed a reduction in *Escherichia coli* UTI	116–118,139
MV140 (Uromune)	rUTI	Licensed in some European countries	56% of MV140 group versus 25% of placebo recipients were UTI free at 6 months	119,140,141
FimCH	rUTI	Phase I trial complete	Reduction in rUTI incidence following vaccination	120
IreA, Hma and other iron-related proteins	uUTI	Preclinical	Reduction in bladder and kidney titres in multiple mouse studies	114,115, 142–144
EbpA, Abp2D	CAUTI	Preclinical	Reduction in bladder and catheter titres in mouse models of CAUTI	45,121,122
Immunomodulatory agents				
NSAIDs	uUTI, rUTI	Multiple RCTs published	Clinically inferior to antibiotics	127
COX2 inhibitors	rUTI	Preclinical	COX2 inhibition reduces rUTI in mice	95,145
IL-1β inhibitor	uUTI, pyelonephritis	Preclinical	Accelerated bacterial clearance and reduced tissue damage in mice	126,128,129
Microbiome therapies				
Faecal microbiota transplants	rUTI	Multiple case series	Reduction in UTI incidence and antimicrobial resistance gene carriage	131–133
Probiotics	rUTI	Additional RCTs needed	Vaginal probiotics reduced rUTI over 10 weeks	84,136
Others				
Methenamine hippurate	rUTI	Additional RCTs needed	Clinically non-inferior to long-term antibiotic prophylaxis for rUTI	146–150
Phage therapy	cUTI, multidrug-resistant infections	Multiple case reports	Clinical cure in seven out of seven patients, bacterial eradication in six out of seven patients	151
Catheter modifications	CAUTI	Preclinical	Reduction in host protein deposition and bacterial colonization by multiple clades	123–125

CAUTI, catheter-associated UTI; CI, confidence interval; cUTI, complicated UTI; NSAIDs, non-steroidal anti-inflammatory drugs; RCT, randomized controlled trial; RR, risk ratio; rUTI, recurrent UTI; UPEC, uropathogenic *Escherichia coli*; UTI, urinary tract infection; uUTI, uncomplicated UTI.

Two recent studies have tested innovative vaccine formulations designed to overcome this limitation. One study has combined recombinant FimH and IutA (an aerobactin receptor precursor) with silk fibroin nanoparticles and demonstrated robust immune responses and protection up to 6 months post immunization[114]. In a second study, the immunogenicity of peptide epitopes from IreA (an outer membrane iron receptor), IutA and IroN (a salmochelin receptor) was improved by linking them to nanofibres containing known T cell epitopes[115]. Interestingly, although serum and urine levels of antigen-specific immunoglobulin G (IgG) and immunoglobulin A (IgA) were robust, IgA was undetectable in faeces, and immunized mice had minimal changes in their gut microbiota compared to unimmunized mice[115]. Because commensal *E. coli* make up part of a healthy gut microbiome, a vaccine strategy that specifically depletes UPEC while leaving commensal *E. coli* intact represents a significant advance.

Vaccines. The UTI vaccine that is currently at the most advanced stage of development is the Janssen 9-valent Extraintestinal Pathogenic *Escherichia Coli* Vaccine (ExPEC9V). ExPEC9V is a conjugated polysaccharide vaccine featuring the O-antigens of nine of the most common *E. coli* serotypes. A phase III clinical trial is currently enrolling patients over 60 years old with a history of UTI and will follow patients for up to 3 years post-vaccination, evaluating a variety of primary and secondary endpoints including time to first UTI, number of UTIs per

participant, and medical resource utilization owing to UTI[116]. An earlier version of this vaccine, which included only four serotypes, was found to reduce the number of rUTIs in a cohort of women with a history of rUTI in a phase Ib trial[117,118]. The results of the ExPEC9V phase III trial are not expected until at least 2025, but if effective, it would represent a significant advance in the prevention of UTIs. Another vaccine, MV140, is a sublingual formulation of inactivated *K. pneumoniae, E. coli, E. faecalis* and *Proteus vulgaris* that has been available in several European countries on a special access and compassionate use basis since 2010 (ref. 119) (Table 1).

In addition, a number of anti-adhesin vaccines have been developed. A vaccine against *E. coli* FimCH recently completed a phase Ia–Ib clinical trial for safety and immunogenicity and found that the vaccine elicited robust FimH-specific antibody responses in all subjects that lasted at least 12 months. Although the study was not designed to evaluate efficacy, a marked reduction in recurrent UTI incidence was observed in patients who received all four doses[120]. Follow-up studies to establish clinical efficacy are planned[120].

Therapeutics for catheter-associated UTIs. As the molecular mechanisms of CAUTI pathogenesis have been unravelled, multiple therapeutic strategies targeting the fibrinogen–pathogen interaction critical to CAUTI pathogenesis have been explored. Vaccines against two fibrinogen-binding adhesins, EbpA from *E. faecalis* and Abp2D from *A. baumannii*, have shown promise in mouse models of CAUTI[45,121,122]. Both vaccines elicit robust antigen-specific IgG responses and reduce bacterial titres by several logs in mouse models of CAUTI. Thus, generating immunity against crucial fibrinogen-binding pili may be an effective strategy for combating this type of infection.

Modifying the catheter itself is also an attractive target for CAUTI prevention strategies. Historically, microbicidal products such as silver-infused or antibiotic-infused catheters have been studied the most, with mixed success[123]. However, more recent approaches have built upon improved understanding of CAUTI pathogenesis and attempt to reduce or eliminate the attachment of host proteins that are a prerequisite for infection. Lipid-infused silicone catheters significantly reduced protein deposition, decreased catheter and bladder bacterial burden of multiple CAUTI pathogens, and prevented systemic dissemination in a mouse model of CAUTI[124]. A co-polymer that was developed specifically to prevent swarming and biomineralization by *P. mirabilis* was shown to reduce fibrinogen deposition in vitro and reduce or eliminate binding by *P. mirabilis*, *E. faecalis*, *E. coli*, *S. aureus* and *P. aeruginosa*[125]. These innovations represent important proof-of-concept that repelling fibrinogen is both technically feasible and effective at reducing bacterial burden. Notably, these catheter modifications are completely antibiotic sparing and cover a range of pathogens commonly found in polymicrobial catheter biofilms. They are also easily scalable and, therefore, have the potential to significantly reduce the clinical burden of CAUTI if brought to market.

Immunomodulation as therapy for UTIs

Immunomodulatory therapy for the treatment and prevention of UTIs has been comprehensively reviewed elsewhere[126]. Briefly, these strategies aim to reduce the initial excessive inflammation associated with UTIs, which contributes to mucosal wounding. The oldest and best-studied immunomodulatory intervention is the use of non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen as an alternative to antibiotics. Unfortunately, although early trials have shown promise, a recent meta-analysis has found that patients treated with NSAIDs had lower tendency to achieve symptom resolution, higher tendency to develop ascending infection and higher tendency to have persistent bacteriuria[127]. Recently, strategies targeting specific mediators of UTI-induced inflammation such as COX2 (Box 1) and interleukin 1β (IL-1β)[128,129] have shown promise in mouse models (Table 1).

Microbiome-targeted therapies

Some therapies discussed in the section 'Pathogen-targeted therapeutics' that were initially investigated in the bladder have also been examined for their ability to deplete UPEC from its gastrointestinal reservoir. Mannosides have been shown to reduce gut levels of UPEC in a mouse model[27], and cranberry consumption has also been investigated and found to have minimal effects on gut microbiome composition[130]. Further, interest in microbiota transplants and probiotics for the treatment of UTIs has grown, spurred in part by interesting incidental findings noted in clinical trials of therapies for other conditions. For example, two studies examining faecal microbiota transplants (FMT) for the treatment of colitis caused by *Clostridium difficile* have found that patients also experienced a reduction in both UTI incidence and carriage of antibiotic resistance genes[131,132]. A small study of 11 women who underwent FMT for the explicit purpose of treating rUTIs has found a nonsignificant decrease in rUTI incidence post-transplant and has also noted a reduction in the carriage of multidrug-resistant microorganisms[133]. Although these data are promising, caution is warranted in all cases of microbiota transplants and thorough donor screening is essential. One case of rUTI in a patient who received FMT was traced to the presence of UPEC in the donor sample, highlighting the unpredictability of the process and the risk of transferring harmful bacteria[134].

All the probiotic strategies attempted have used *Lactobacillus* species, with the implicit goal of restoring a healthy vaginal bacterial community that will exclude uropathogens. Oral *Lactobacillus* spp. probiotics are capable of establishing vaginal colonization and can reverse the microbiologic features of bacterial vaginosis[135]. However, the utility of oral probiotics for the treatment of recurrent UTIs is uncertain. More success has been reported when probiotics are delivered as vaginal suppositories. One study with a well-characterized *L. crispatus* strain has achieved vaginal colonization over 10 weeks and reduced the incidence of rUTI[136]. Additional, high-quality randomized controlled trials with well-characterized and replicable *Lactobacillus* species will be required to fully evaluate both oral and vaginal probiotic strategies.

Conclusions and outlook

UTIs are a major source of morbidity, mortality and antibiotic use, which collectively cost billions of dollars annually and contribute to the rise of antimicrobial resistance. Intensive research into the bacterial and host factors that contribute to UTI pathogenesis has paved the way for precisely targeted novel therapeutic strategies, including vaccines and small molecule inhibitors against pili and siderophores, immunomodulatory therapies, and probiotics, that have the potential to revolutionize UTI treatment and prevention.

As we look towards the future of UTI research, existing knowledge about mechanisms of pathogenesis can serve as building blocks for larger questions about UTI syndromes. One area that has yet to be fully explored is the interplay of the gut–vagina–bladder axis. The gut and vaginal microbiota are both complex and dynamic ecosystems, and a growing body of evidence suggests a role for the urinary microbiome as well. Human studies that sample all three compartments, both deeply and longitudinally, will be required to reveal the relationships between

the microbiota, the bladder and the host immune system. A second area of open question is the role of adaptive immunity in UTIs. Unlocking the puzzling reasons why adaptive immunity so often fails and allows same-strain UTI recurrences will pave the way for immunomodulatory therapies to help patients with rUTI escape the cycle of symptoms, antibiotics and recurrence.

To realize the full promise of UTI research, continued investment in the clinical translation of discoveries is essential. Currently, several innovative strategies have been tested only in animal models or have stalled in spite of encouraging initial human studies. More rapid development of approved UTI therapies will both reduce the considerable human suffering associated with UTIs and improve the resilience of our health-care systems against the encroaching threat of antimicrobial resistance.

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The authors contributed equally to all aspects of the article.

Competing interests
S.J.H. has an ownership interest in Fimbrion Therapeutics and may benefit if the company is successful in marketing mannosides. S.J.H. is also the chief scientific officer of QureTech Bio. S.J.H. is an inventor on multiple patents pertaining to urinary tract infection therapeutics including the FimCH and EbpA vaccines. M.R.T. and S.J.H are inventors on a patent for the Abp2D vaccine. S.K.R. declares no competing interests.

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